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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,424	03/01/2002	Phillip Dan Cook	ISIS-5031	4700

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WOODCOCK WASHBURN LLP
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EXAMINER

EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/087,424

Applicant(s)

COOK, PHILLIP DAN

Examiner

Jon D Epperson

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 March 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-33,35-40,42-46 and 48-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-33,35-40,42-46 and 48-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Please note: There is a change in Examiner handling prosecution in this case from Maurie Baker to Jon Epperson.

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/1/04 has been entered. Claims 31-50 were pending. Applicants canceled claims 34, 41 and 47. Applicants further amended claims 31, 38 and 45. Therefore, claims 31-33, 35-40, 42-46 and 48-50 are pending and active in the instant application. An action on the merit follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All outstanding objections and/or rejections are withdrawn in view of Applicants' amendments and/or arguments.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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3. Claims 31, 38 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claims 31, 38 and 45** recite inconsistent chemical nomenclature, which renders the claim vague and indefinite. For example, Applicants use $\text{-NH(R}^1\text{)NH-}$ and $\text{-NHR}^2\text{NH-}$ for the T moiety. It is not clear what function the “()” serve for the R^1 group? If Applicants intend for the R^1 group to be bound between both NH groups as shown for the R^2 then it would appear that the brackets are unnecessary. Applicants are requested to clarify and/or correct.

B. **Claims 31, 38 and 45** recite the phrase “or via a tether moiety” in the last line of said claims. The Examiner contends that this statement is inconsistent with the formulas shown in said claims because the formulas require a tether moiety i.e., it is not an option and thus the word “or” cannot be used to further limit the claim. Applicants are requested to clarify and/or correct

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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4. Claims 31-33, 35-40, 42-46 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norman et al. (Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. "A Structure-Based Library Approach to Kinase Inhibitors" *J. Am. Chem. Soc.* **1996**, *118*, 7430-7431) and Gordeev et al. (WO 96/33972, of record) and Konings et al. (Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. "Deconvolution of Combinatorial Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies" *J. Med. Chem.* **1996**, *39*, 2710-2719) and Siani et al. (Siani, M. A.; Weininger, D.; James, C. A.; Blaney, J. M. "CHORTLES: A Method for Representing Oligomeric and Template-Based Mixtures" *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 1026-1033) and Carell et al. (Carell, T.; Wintner, E. A.; Rebek, J. "A Solution-Phase Screening Procedure for the Isolation of Active Compounds from a Library of Molecules" *Angew Chem. Int. Ed. Engl.* **1994**, *33*(20), 2061-2064).

For *claims 31, 38, and 45*, Norman et al. (see entire document) disclose methods for making a library of Kinase Inhibitors (see Norman et al, abstract), which reads on claims 31, 38 and 45. For example, Norman et al. disclose contacting a purine heterocyclic scaffold having at least two functionalizable atoms, wherein at least one of said functionalizable atoms is blocked, with a mixture of at least six different chemical substituents to append each of said chemical substituents to said heterocyclic scaffold directly to form a substituent-appended scaffold (e.g., see page 7431, scheme 2, wherein the scaffold is represented by any of compounds **9-11**; see also page 7431, column 2, paragraph 1; see also Supplementary material pages 8-9). In this scenario, the blocking agent is the trifluoroacetic anhydride in step (e) of Scheme 2 and the at least two functionalizable groups are, for example, the -NH₂, C-Cl, CH₂CH₂O of compound **9** in

Scheme 2. There is also a “deblocking” step in this reaction scheme (e.g., see Scheme 2, step (f) wherein the $F_3C-C(=O)$ is removed). Norman et al. also disclose contacting the substituent scaffold with a mixture of at least six different chemical substituents to append each of said chemical substituents to said substituent-appended scaffold either directly or via a tether moiety covalently attached to one of said functionalizable atoms (e.g., see page 7431, column 2, paragraph 1, “Following this, a small library of 16 alkylated aminopurines was prepared ... using primary and benzylic alcohols”). Finally, the compounds made by the procedure shown in Scheme 2 read on Applicants’ purine structure in claim 1. For example, purine **12c** (see page 9 of Supplementary Material) possesses $-NH-CH_2-Ph-Br$, $-NH-CH_2-Ph$ and $-CH_2CH_2OH$ as purine substituents at the 2, 6 and 9 positions, respectively. Both the $-NH-CH_2-Ph-Br$ and $-NH-CH_2-Ph$ groups have, for example, an “NH” tether and a “substituted C_6-C_{14} aryl” L group. The $-CH_2-CH_2-OH$ has, for example, an “OR³” tether and “hydrogen” L group. Please note that many other “equivalent” substituents have been used at positions 2 and 6 of the purine that also read on Applicants’ claimed structure (e.g., supplementary material, page 9, Purines **12a** and **12b**; see also Amines 58 that also can be used).

For *claims 35-36, 42-43, 48-49*, Norman et al. teach at least ten or fifteen different chemical substituents (e.g., see page 7431, column 2, paragraph 1, “Following this, a small library of 16 alkylated aminopurines was prepared ... using primary and benzylic alcohols”; see also page 9, Supplementary Materials, especially amines **58**).

The prior art teachings of Norman et al differ from the claimed invention as follows:

For *claims 31, 38 and 45*, Norman et al. do not teach contacting the scaffold with a “mixture” of substituents. Norman et al. teach contacting the substituents “separately” using an array of Geysen pins and a microtiter plate i.e., “one compound, one well” (see Norman et al, Supplementary Information, page 10, paragraph 1).

For *claims 32, 33, 39, 40, 46*, Norman et al. do not teach using 20 mole percent equimolarity or carrying out the contacting steps in one reaction vessel.

For *claims 37, 44 and 50*, Norman et al. do not teach performing the reactions in solution phase.

However, Gordeev et al. and Konings et al. and Siani et al. and Carell et al. teach the following limitations that are deficient in Norman et al.:

For *claims 31-33, 37-40 and 44-46 and 50*, Gordeev et al. and Konings et al. and Siani et al. (see entire documents) teach the use of a “mixture” of substituents within 20 mole percent equimolarity wherein the reaction is carried out in one reaction vessel and in solution phase. For example, Gordeev et al. teach combinatorial methods for creating libraries of heterocyclic aromatic compounds and, as a result, the references represent analogous art. The library of compounds disclosed by Gordeev et al. has a heterocyclic scaffold (see page 34-35 and more specifically page 81) and are substantially homogeneous (page 35, bottom). The library of compounds are made in a pooled format (see page 84, lines 18-28), for example, a pool (i.e., a mixture) of 21 pyrimidines is made and tested. This reads on the limitation of a mixture of at least 6 compounds. All compounds are present in at least some of the pools and the compounds are synthesized at a purity (see page 81) that is close to equimolarity.

In addition, Konings et al. state, “[s]ynthesis and testing of mixtures of compounds [referred to herein as mixing technology] in a combinatorial library allow much greater throughput than synthesis and testing of individual compounds [e.g., individual synthesis using Geysen pins]” (e.g., see Konings et al. abstract) and also state that this mixing technology is generally applicable to a “variety of chemistries” (e.g., see Konings et al. page 2710, column 1, paragraph 2; see also figure 2 wherein the screening of a library of 27 compounds is shown). Furthermore, Siani et al. disclose that mixing technology is particularly well suited for “fixed templates (e.g., rings)”, which would encompass the fixed template “purine rings” of Norman et al. (e.g., see Siani et al., abstract). Finally, Carell et al. teach that mixtures can be produced and/or screened in solution (e.g., see entire document, especially figure 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create a mixture (i.e. library) of six or more compounds of the claimed type as disclosed by Norman et al. using the “mixing” technology as taught by Gordeev et al., Konings et al., Siani et al. and Carell et al. because the method of forming and/or screening a library (e.g., using Geysen pins/microtiter plates disclosed by Norman et al. versus the mixing technology disclosed by Gordeev et al., Konings et al., Siani et al. and Carell et al.) represents a mere design choice (i.e., both methods were well known in the art at the time of filing and could be used interchangeably to produce and/or screen libraries of heterocyclic aromatic compounds as exemplified above). A person of ordinary skill in the art would have been motivated to use the mixing technology as exemplified by Gordeev et al., Konings et al., Siani et al. and Carell et al. to create and/or screen a larger

number of compounds in a shorter period of time than could be achieved using the “one compound, one well” approach employed by Norman et al. (e.g., see Konings et al., page 2710, column 1, paragraph 1, “Synthesis and testing of mixtures of compounds in a combinatorial library offer the potential of much greater throughput than the ‘one compound, one well’ approach”; see also abstract). Furthermore, a person of ordinary skill in the art would have had a reasonable expectation of success because Konings et al. state that the method is generally applicable to all compounds and Siani et al. further state that the mixing technology is particularly well suited for fixed template ring structures (e.g., see Konings et al., page 2710, column 1, paragraph 2; see also Siani et al., abstract), which would include the fixed template “purine ring” structures disclosed by Norman et al. (i.e., the references teach toward Applicants’ claimed compounds).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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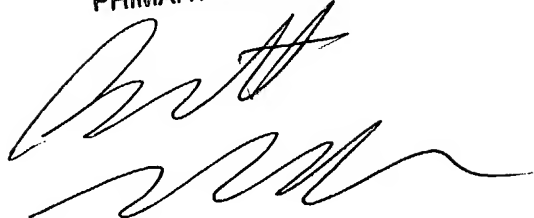
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Jon D. Epperson, Ph.D.

May 19, 2004

BENNETT CELSA
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Bennett Celsa', written over the printed name and title.